IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 10/528,139
Applicant : Jochen KNOLLE et al
Filed : July 8, 2005
TC/A.U. : 1646
Examiner :

Docket No. : 2918-108
Customer No. : 6449
Confirmation No.: 2799

REQUEST FOR REPUBLICATION OF PUBLISHED APPLCIATION UNDER 37 CFR§1.221(b) DUE TO OFFICE ERROR

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

It is requested that the Office republish the above-identified application due to errors in the published claims, such errors being on the part of the Patent and Trademark Office. The errors are shown on the attached copy of the involved claims 184, 216, 217 and 224 with the corrections hand written beside the error. This request is being timely filed, and should be granted so that no question of the published claims content can arise in the future.

Since the errors are the fault of the Office, no fee appears to be necessary. However, if any fee is required, kindly charge our Deposit Account 02-2135.

Respectfully submitted,

By

Robert B. Murray
Attorney for Applicant
Registration No. 22,980
ROTHWELL, FIGG, ERNST & MANBECK
1425 K. Street, Suite 800
Washington, D.C. 20005
Telephone: (202) 783-6040

RBM/cb

Biosciences) diluted to 1 μg/ml in blocking buffer. Blots were washed 3×10 min with 10 mM Tris (pH 7.5), 100 mM NaCl, 0.1% Tween-20 (washing buffer) and incubated with 0.7 μg/ml peroxidase-conjugated sheep anti-mouse IgG (Sigma) in blocking buffer for 1 h. After washing 3×10 min with washing buffer, the plot was developed with the ECL+ detection kit (Amersham Biosciences).

[0451] Of particular relevance are compounds 30, 102, 264, 399, 629, 639, 657, 673.

EXAMPLE 40

DAPI Staining

[0452] In order to show that the compounds according to the present invention are actually useful for inducing apoptosis in tumor cells, DAPI staining was performed.

[0453] Hela cells grown on poly-L-Lys-coated coverslips were fixed with 2% paraformaldehyde/MeOH.

[0454] Cellular DNA was stained with DAPI staining buffer (100 mM Tris (pH 7.4), 150 mM NaCl, 1 mM $CaCl_2$, 0.5 mM $MgCl_2$, 0.1% nonidet P-40, 1 μg/ml DAPI (Molecular Probes)). All the steps were performed at room temperature, and cells were washed two times with PBS after each step. Finally, cells were mounted in 80% glycerol/PBS.

[0455] As may be taken from FIG. 3 compounds 30, 102, 264 and 399 induce apoptosis in tumor cells.

[0456] The features of the present invention disclosed in the specification, the claims and/or the drawing may both separately and in any combination thereof be material for realizing the invention in various forms thereof.

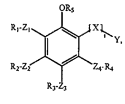
LENGTHY TABLE

The patent application contains a lengthy table section. A copy of the table is available in electronic form from the USPTO web site (http://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US20070054904A1). An electronic copy of the table will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

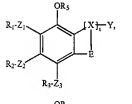
1-183. (canceled)

184. A compound of the formula (I), (II), (III), (IV), (V):

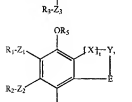
I



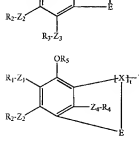
II



III



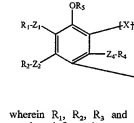
IV



or

-continued

V



wherein R_1, R_2, R_3 and R_4 are each independently selected from the group comprising H, OR_6, SR_7, NR_8R_9, halo, alkyl, substituted alkyl, alkylaryl, substituted alkylaryl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, substituted alkylcycloalkyl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, alkylheterocyclyl, substituted alkylheterocyclyl, heteroaryl, substituted heteroaryl, alkylheteroaryl and substituted alkylheteroaryl;

wherein R_1 and R_2, R_2 and R_3, R_3 and R_4, R_1 and R_3, R_1 and R_4 and R_2 and R_4 may be linked so as to form a ring comprising 4 to 12 members, preferably 5 to 10 members,

wherein Z_1, Z_2, Z_3 and Z_4 are each and independently selected from the group comprising —C(O)—, —C(S)—, —C(O)—NR_{10}—, —C(S)NR_{11}—, —C(N—CN)—NR_{12}—, —S(O)—, —$S(O_2)$—, —S(O)—NR_{13}—, and —$S(O_2)$—NR_{14}—, —O—, —S— or are each and individually absent;

R_5 is selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, substituted alkylcycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, heterocyclyl,

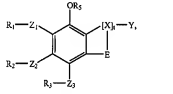
R_{16}, R_{17}, R_{18}, R_{19}, R_{20} and R_{21} are each and independently selected from the group comprising H, alkyl, substituted alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, alkoxy, substituted alkoxy, aryloxy, substituted aryloxy, alkylamino, substituted alkylamino, arylamino and substituted arylamino;

wherein Y is selected from the group comprising alkyl, substituted alkyl, straight alkyl, substituted straight alkyl, branched alkyl, substituted branched alkyl, straight alkenyl, substituted straight alkenyl, branched alkenyl, substituted branched alkenyl, straight alkynyl, substituted straight alkynyl, branched alkynyl, substituted branched alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclyl, substituted heterocyclyl, mono-unsaturated heterocyclyl, poly-unsaturated heterocyclyl, mono-substituted poly-unsaturated heterocyclyl, poly-substituted poly-unsaturated heterocyclyl, mono-substituted mono-unsaturated heterocyclyl, poly-substituted mono-unsaturated heterocyclyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, wherein Y is different from a peptide or is absent;

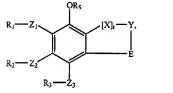
185. The compound according to claim 184, wherein the phenol moiety forms a cyclic structure with the spacer X and/or Y.

186. The compound according to claim 184, wherein the compound is

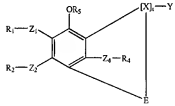
II



III

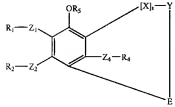


IV



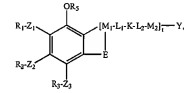
or

V

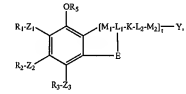


187. The compound according to claim 184, wherein the compound is

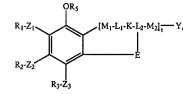
VI



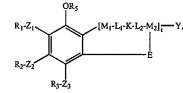
VII



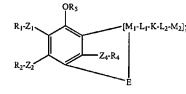
VIII



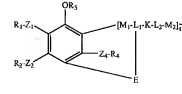
IX



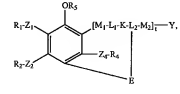
X



XI



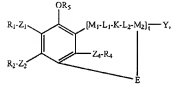
XII



or

-continued

XIII



188. The compound according to claim 184, wherein K is C=T.

189. The compound according to claim 188, wherein T is selected from the group comprising O and S.

190. The compound according to claim 189, wherein T is O.

191. The compound according to claim 189, wherein T is S.

192. The compound according to claim 189, wherein T is N—CN, N—NO_2, CH—NO_2 or N—R*.

193. The compound according to claim 184, wherein L1 and L2 are each independently a primary amine, preferably NR^e and/or NR^d.

194. The compound according to claim 184, wherein n=0 and m is any integer from 0 to 10.

195. The compound according to claim 184, wherein R_1 and/or R_3 are selected from the group comprising halo, alkyl, substituted alkyl, heterocyclyl, substituted heterocyclyl, heteroaryl and substituted heteroaryl, preferably R_1 is halo.

196. The compound according to claim 184, wherein R_5 is selected from the group comprising H and —C(O)-Q,

wherein preferably Q is selected from alkylheterocyclyl and substituted alkylheterocyclyl, preferably N-acylated morpholino- and/or N-acylated piperazino- and/or N-acyl-derivatives.

197. The compound according to claim 184, wherein R_6 is alkyl or substituted alkyl.

198. The compound according to claim 184, wherein R_8 and R_9 are individually and separately selected from the group comprising H, alkyl and substituted alkyl.

199. The compound according to claim 184, wherein n and m are individually and independently any integer from 1 to 3.

200. The compound according to claim 184, wherein n is any integer from 0 to 3 and is preferably 0 or 1.

201. The compound according to claim 184, wherein n and m are both 0.

202. The compound according to claim 184, wherein t is 1 or 2.

203. The compound according to claim 184, wherein R^c and/or R^d are each and independently from each other selected from the group comprising alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, substituted alkylcycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, heterocyclyl, substituted heterocyclyl, alkylheterocyclyl, substituted alkylheterocyclyl, heteroaryl, substituted heteroaryl, alkylheteroaryl and substituted alkylheteroaryl.

204. The compound according to claim 184, wherein R^a, R^b, R^f and R^g are each individually and independently from each other selected from the group comprising H, OR_{17}, SR_{18}, $NR_{19}R_{20}$, halo, alkyl and substituted alkyl.

205. The compound according to claim 184, wherein Y is selected from the group comprising alkyl, substituted alkyl, straight alkyl, substituted straight alkyl, branched alkyl, substituted branched alkyl, straight alkenyl, substituted straight alkenyl, branched alkenyl, substituted branched alkenyl, straight alkynyl, substituted straight alkynyl, branched alkylnyl and substituted branched alkynyl.

206. The compound according to claim 184, wherein Y is selected from the group comprising cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclyl, substituted heterocyclyl, mono-unsaturated heterocyclyl, poly-unsaturated heterocyclyl, mono-substituted poly-unsaturated heterocycyl, poly-substituted poly-unsaturated heterocyclyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, wherein Y is different from a peptide or is absent.

207. The compound according to claim 184, wherein X is

$$—(CR^aR^b)_n—NR^e—CZ-NR^d—(CR^fR^g)_m—$$

and Z is selected from the group comprising O, S, N—CN, N—NO_2 and CH—NO_2.

208. The compound according to claim 207, wherein m is any integer from 1 to 10.

209. The compound according to claim 207, wherein R_5 is selected from the group comprising H and —C(O)-Q.

210. The compound according to claim 209, wherein R_5 is H.

211. The compound according to claim 209, wherein n is 0.

212. The compound according to claim 207, wherein n is any integer from 1 to 10.

213. The compound according to 184, wherein t is 1.

214. The compound according to claim 184, wherein Y is selected from the group comprising alkyl, substituted alkyl, straight alkyl, substituted straight alkyl, branched alkyl, substituted branched alkyl, straight alkenyl, substituted straight alkenyl, branched alkenyl, substituted branched alkenyl, straight alkynyl, substituted straight alkynyl, branched alkynyl and substituted branched alkynyl.

215. The compound according to claim 184, wherein Y is selected from the group comprising cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkcnyl, heterocyclyl, substituted heterocyclyl, mono-unsaturated heterocyclyl, poly-unsaturated heterocyclyl, mono-substituted poly-unsaturated heterocyclyl, poly-substituted poly-unsaturated heterocyclyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, wherein Y is different from a peptide or wherein Y is absent.

216. The compound according to claim 207, wherein R_c and/or R^d are independently from each other selected from the group alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, substituted alkylcycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, heterocyclyl, substituted heterocyclyl, alkylheterocyclyl, substituted alkylheterocyclyl, heteroaryl, substituted heteroaryl, alkylheteroaryl and substituted alkylheteroaryl.

217. A compound according to claim 184, wherein X is

$$—(CR^aR^b)_n—(NR_c)—(CR^fR^g)_m—$$

218. The compound according to claim 217, wherein R_5 is selected from the group comprising H and —C(O)-Q.

219. The compound according to claim 218, wherein R_5 is H.

220. The compound according to claim 217, wherein m is any integer between 1 and 10.

221. The compound according to claim 220, wherein n is 0.

222. The compound according to claim 220, wherein R_5 is selected from the group comprising H and —C(O)-Q.

223. The compound according to claim 222, wherein R_5 is H.

224. A compound according to claim 217, wherein X is $-(CR^aR^b)_n-NR^a-(CR^fR^g)_t-$, and wherein t is 1.

225. The compound according to claim 224, wherein Y is selected from the group comprising alkyl, substituted alkyl, straight alkyl, substituted straight alkyl, branched alkyl, substituted branched alkyl, straight alkenyl, substituted straight alkenyl, branched alkenyl, substituted branched alkenyl, straight alkynyl, substituted straight alkynyl, and substituted branched alkynyl.

226. The compound according to claim 225, wherein R_5 is selected from the group comprising H and —C(O)-Q.

227. The compound according to claim 226, wherein R_5 is H.

228. The compound according to claim 225, wherein n is 0.

229. The compound according to claim 224, wherein m is any integer between 1 and 10.

230. The compound according to claim 224, wherein m is any integer between 2 and 10.

231. The compound according to claim 229, wherein R_5 is selected from the group comprising H and —C(O)-Q.

232. The compound according to claim 231, wherein R_5 is H.

233. The compound according to claim 229, wherein Y is selected from the group comprising cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclyl, substituted heterocyclyl, mono-unsaturated heterocyclyl, poly-unsaturated heterocyclyl, mono-substituted poly-unsaturated heterocyclyl, poly-substituted poly-unsaturated heterocyclyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, wherein Y is different from a peptide or is absent.

234. The compound according to claim 233, wherein R_5 is selected from the group comprising H and —C(O)-Q.

235. The compound according to claim 234, wherein R_5 is H.

236. The compound according to claim 233, wherein n is 0.

237. A compound according to claim 184, wherein X is

$$-(CR^aR^b)_n-NR^a-Z-(CR^fR^g)_m-$$

and can be inserted in any orientation into any of the preceding formulae,

and wherein Z is selected from the group comprising C(O), C(S), $S(O_2)$, C(O)—O, and C(O)—S.

238. The compound according to claim 237, wherein R_5 is selected from the group comprising H and —C(O)-Q.

239. The compound according to claim 233, wherein R_5 is H.

240. The compound according to claim 238, wherein n is 0.

241. The compound according to claim 237, wherein X is

$$-(CR^aR^b)_n-NR^a-Z-(CR^fR^g)_m-$$

and can be inserted in any orientation into any of the preceding formulae,

and Z is selected from the group comprising C(O), C(S), $S(O_2)$, C(O)—O, and C(O)—S, and wherein preferably t is 1.

242. The compound according to claim 241, wherein Y is selected from the group comprising alkyl, substituted alkyl, straight alkyl, substituted straight alkyl, branched alkyl, substituted branched alkyl, straight alkenyl, substituted straight alkenyl, branched alkenyl, substituted branched alkenyl, straight alkynyl, substituted straight alkynyl, and substituted branched alkynyl.

243. The compound according to claim 242, wherein R_5 is selected from the group comprising H and —C(O)-Q.

244. The compound according to claim 243, wherein R_5 is H.

245. The compound according to claim 242, wherein n is 0.

246. The compound according to claim 241, wherein m is any integer between 1 and 10.

247. The compound according to claim 246, wherein R_5 is selected from the group comprising H and —C(O)-Q.

248. The compound according to claim 247, wherein R_5 is H.

249. The compound according to claim 246, wherein Y is selected from the group comprising cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclyl, substituted heterocyclyl, mono-unsaturated heterocyclyl, poly-unsaturated heterocyclyl, mono-substituted poly-unsaturated heterocyclyl, poly-substituted poly-unsaturated heterocyclyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, wherein Y is different from a peptide or is absent.

250. The compound according to claim 249, wherein R_5 is selected from the group comprising H and —C(O)-Q.

251. The compound according to claim 250, wherein R_5 is H.

252. The compound according to claim 249, wherein n is 0.

253. The compound according to claim 229, wherein m is any integer between 2 and 10.

254. The compound according to claim 253, wherein R_5 is selected from the group comprising H and —C(O)-Q.

255. The compound according to claim 254, wherein R_5 is H.

256. The compound according to claim 248, wherein n is 0.

257. Compound, preferably a compound according to claim 184, selected from:

3-[3-(5-Chloro-2-hydroxy-phenyl)-ureido]-propionic acid ethyl ester

1-(5-Chloro-2-hydroxy-phenyl)-3-pentyl-urea

1-Benzyl-3-(5-chloro-2-hydroxy-phenyl)-urea

1-(5-Chloro-2-hydroxy-phenyl)-3-(2-methyl-benzyl)-urea

1-(5-Chloro-2-hydroxy-phenyl)-3-phenethyl-urea

1-(5-Chloro-2-hydroxy-phenyl)-3-(1,1,3,3-tetramethyl-butyl)-urea

1-tert-Butyl-3-(5-chloro-2-hydroxy-phenyl)-urea

1-(5-Chloro-2-hydroxy-phenyl)-3-cyclohexylmethyl-urea